

We Claim:

1. A bisubstrate inhibitor of insulin receptor kinase, comprising:
a nucleotide or nucleotide analog moiety;
and a peptide moiety;
wherein said moieties are linked by a tether that comprises a proton donor, wherein the tether is ≥ 4.9 Å measured from a gamma phosphorus of the nucleotide or nucleotide analog moiety to the proton donor.
2. The bisubstrate inhibitor of claim 1 wherein the nucleotide or nucleotide analog moiety is ATP.
3. The bisubstrate inhibitor of claim 1 wherein the nucleotide or nucleotide analog moiety is γ -S-ATP.
4. The bisubstrate inhibitor of claim 1 wherein the peptide comprises a tyrosine residue in which its phenolic oxygen is replaced with a nitrogen atom.
5. The bisubstrate inhibitor of claim 1 wherein the peptide moiety has at least 4 contiguous amino acid residues selected from the sequence Lys, Lys, Lys, Leu, Pro, Ala, Thr, Gly, Asp, Tyr, Met, Asn, Met, Ser, Pro, Val, Gly, Asp (SEQ ID NO:1).
6. The bisubstrate inhibitor of claim 1 wherein the peptide moiety has at least 5 contiguous amino acid residues selected from the sequence Lys, Lys, Lys, Leu, Pro, Ala, Thr, Gly, Asp, Tyr, Met, Asn, Met, Ser, Pro, Val, Gly, Asp (SEQ ID NO:1).
7. The bisubstrate inhibitor of claim 1 wherein the peptide moiety comprises the sequence Lys, Lys, Lys, Leu, Pro, Ala, Thr, Gly, Asp, Tyr, Met, Asn, Met, Ser, Pro, Val, Gly, Asp (SEQ ID NO:1).
8. The bisubstrate inhibitor of claim 1 wherein the nucleotide or nucleotide analog moiety is a nucleotide in which one or more phosphate groups are replaced by uncharged alkyl groups.

9. The bisubstrate inhibitor of claim 1 wherein the nucleotide or nucleotide analog moiety is a nucleotide in which one or more phosphate groups are replaced by uncharged C₁ to C₃ alkyl groups.
10. The bisubstrate inhibitor of claim 1 wherein the peptide moiety comprises a membrane translocating sequence (MTS).
11. The bisubstrate inhibitor of claim 10 wherein the MTS is at the N-terminus of the peptide moiety.
12. The bisubstrate inhibitor of claim 10 wherein the MTS is at the C-terminus of the peptide moiety.
13. The bisubstrate inhibitor of claim 1 wherein the peptide moiety comprises an HIV TAT sequence.
14. The bisubstrate inhibitor of claim 1 wherein the peptide moiety comprises carbon-carbon bonds in place of amide bonds.
15. The bisubstrate inhibitor for the insulin receptor tyrosine kinase of claim 1 which is Compound 2.
16. A method of inhibiting insulin receptor kinase (IRK) comprising:
contacting IRK with a bisubstrate inhibitor comprising a nucleotide or nucleotide analog moiety and a peptide moiety, wherein said moieties are linked by a tether that comprises a proton donor, wherein the tether is ≥ 4.9 Å measured from a gamma phosphorus of the nucleotide or nucleotide analog to the proton donor, whereby the IRK is competitively inhibited.
17. The method of claim 16 wherein the nucleotide or nucleotide analog moiety is ATP.
18. The method of claim 16 wherein the nucleotide or nucleotide analog moiety is γ S-ATP.
19. The method of claim 16 wherein the peptide comprises a tyrosine residue in which its phenolic oxygen is replaced with a nitrogen atom.
20. The method of claim 16 wherein the peptide moiety has at least 4 contiguous amino acid residues selected from the sequence Lys, Lys, Lys, Leu,

Pro, Ala, Thr, Gly, Asp, Tyr, Met, Asn, Met, Ser, Pro, Val, Gly, Asp
(SEQ ID NO:1).

21. The method of claim 16 wherein the peptide moiety has at least 5 contiguous amino acid residues selected from the sequence Lys, Lys, Lys, Leu, Pro, Ala, Thr, Gly, Asp, Tyr, Met, Asn, Met, Ser, Pro, Val, Gly, Asp (SEQ ID NO:1).
22. The method of claim 16 wherein the peptide moiety comprises the sequence Lys, Lys, Lys, Leu, Pro, Ala, Thr, Gly, Asp, Tyr, Met, Asn, Met, Ser, Pro, Val, Gly, Asp (SEQ ID NO:1).
23. The method of claim 16 wherein the nucleotide or nucleotide analog moiety is a nucleotide in which one or more phosphate groups are replaced by uncharged alkyl groups.
24. The method of claim 16 wherein the nucleotide or nucleotide analog moiety is a nucleotide in which one or more phosphate groups are replaced by uncharged C1 to C4 alkyl groups.
25. The method of claim 16 wherein the peptide moiety comprises a membrane translocating sequence (MTS).
26. The method of claim 25 wherein the MTS is at the N-terminus of the peptide moiety.
27. The method of claim 25 wherein the MTS is at the C-terminus of the peptide moiety.
28. The method of claim 16 wherein the peptide moiety comprises an HIV TAT sequence.
29. The method of claim 16 wherein the peptide moiety comprises carbon-carbon bonds in place of amide bonds.
30. A bisubstrate inhibitor of protein kinase A (PKA) comprising:
a nucleotide or nucleotide analog moiety; and
a peptide moiety;

wherein said moieties are linked by a tether that comprises a proton donor, wherein the tether is ≥ 4.9 Å measured from a gamma phosphorus of the nucleotide or nucleotide analog to the proton donor.

31. The bisubstrate inhibitor of claim 30 wherein the nucleotide or nucleotide analog moiety is ATP.
32. The bisubstrate inhibitor of claim 30 wherein the nucleotide or nucleotide analog moiety is γ S-ATP.
33. The bisubstrate inhibitor of claim 30 wherein the peptide comprises a diaminopropionic acid residue.
34. The bisubstrate inhibitor of claim 30 wherein the peptide moiety has at least 4 contiguous amino acid residues selected from the sequence Leu, Arg, Arg, Ala, diaminopropionic acid, Leu, Gly (SEQ ID NO:2).
35. The bisubstrate inhibitor of claim 30 wherein the peptide moiety has at least 5 contiguous amino acid residues selected from the sequence Leu, Arg, Arg, Ala, diaminopropionic acid, Leu, Gly (SEQ ID NO:2).
36. The bisubstrate inhibitor of claim 30 wherein the peptide moiety comprises the sequence Leu, Arg, Arg, Ala, diaminopropionic acid, Leu, Gly (SEQ ID NO:2).
37. The bisubstrate inhibitor of claim 30 wherein the nucleotide or nucleotide analog moiety is a nucleotide in which one or more phosphate groups are replaced by uncharged alkyl groups.
38. The bisubstrate inhibitor of claim 30 wherein the nucleotide or nucleotide analog moiety is a nucleotide in which one or more phosphate groups are replaced by uncharged C₁ to C₃ alkyl groups.
39. The bisubstrate inhibitor of claim 30 wherein the peptide moiety comprises a membrane translocating sequence (MTS).
40. The bisubstrate inhibitor of claim 39 wherein the MTS is at the N-terminus of the peptide moiety.
41. The bisubstrate inhibitor of claim 39 wherein the MTS is at the C-terminus of the peptide moiety.

42. The bisubstrate inhibitor of claim 30 wherein the peptide moiety comprises an HIV TAT sequence.
43. The bisubstrate inhibitor of claim 30 wherein the peptide moiety comprises carbon-carbon bonds in place of amide bonds.
44. A method of inhibiting protein kinase A (PKA) comprising:
contacting PKA with a bisubstrate inhibitor comprising a nucleotide or nucleotide analog moiety and a peptide moiety, wherein said moieties are linked by a tether that comprises a proton donor, wherein the tether is ≥ 4.9 Å measured from a gamma phosphorus of the nucleotide or nucleotide analog to the proton donor, whereby the PKA is competitively inhibited.
45. The method of claim 44 wherein the nucleotide or nucleotide analog moiety is ATP.
46. The method of claim 44 wherein the nucleotide or nucleotide analog moiety is γ S-ATP.
47. The method of claim 44 wherein the peptide comprises a diaminopropionic acid residue.
48. The method of claim 44 wherein the peptide moiety has at least 4 contiguous amino acid residues selected from the sequence Leu, Arg, Arg, Ala, diaminopropionic acid, Leu, Gly (SEQ ID NO:2).
49. The method of claim 44 wherein the peptide moiety has at least 5 contiguous amino acid residues selected from the sequence Leu, Arg, Arg, Ala, diaminopropionic acid, Leu, Gly (SEQ ID NO:2).
50. The method of claim 44 wherein the peptide moiety comprises the sequence Leu, Arg, Arg, Ala, diaminopropionic acid, Leu, Gly (SEQ ID NO:2).
51. The method of claim 44 wherein the nucleotide or nucleotide analog moiety is a nucleotide in which one or more phosphate groups are replaced by uncharged alkyl groups.

52. The method of claim 44 wherein the nucleotide or nucleotide analog moiety is a nucleotide in which one or more phosphate groups are replaced by uncharged C1 to C4 alkyl groups.
53. The method of claim 44 wherein the peptide moiety comprises a membrane translocating sequence (MTS).
54. The method of claim 53 wherein the MTS is at the N-terminus of the peptide moiety.
55. The method of claim 53 wherein the MTS is at the C-terminus of the peptide moiety.
56. The method of claim 44 wherein the peptide moiety comprises an HIV TAT sequence.
57. The method of claim 44 wherein the peptide moiety comprises carbon-carbon bonds in place of amide bonds.
58. The bisubstrate inhibitor of claim 1 which is bound to insulin receptor kinase.
59. The bisubstrate inhibitor of claim 32 which is bound to protein kinase A.
60. A bisubstrate inhibitor of a protein kinase comprising:
 - a nucleotide or nucleotide analog moiety; and
 - a peptide moiety;wherein said moieties are linked by a tether that comprises a proton donor, wherein the tether is ≥ 4.9 Å measured from a gamma phosphorus of the nucleotide or nucleotide analog to the proton donor.
61. The bisubstrate inhibitor of claim 60 wherein the protein kinase is a serine protein kinase.
62. The bisubstrate inhibitor of claim 60 wherein the protein kinase is a threonine protein kinase.
63. The bisubstrate inhibitor of claim 60 wherein the protein kinase is a tyrosine protein kinase.
64. The bisubstrate inhibitor of claim 61 wherein a nitrogen atom replaces a hydroxyl oxygen on the serine.

65. The bisubstrate inhibitor of claim 62 wherein a nitrogen atom replaces a hydroxyl oxygen on the threonine.
66. The bisubstrate inhibitor of claim 63 wherein a nitrogen atom replaces a hydroxyl oxygen on the tyrosine.
67. The bisubstrate inhibitor of claim 60 which is bound to the protein kinase.
68. The bisubstrate inhibitor of claim 30 which has the structure of Compound 4.

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